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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/590,421 | 09/08/2008 | David Ray Filpula | 213.1204-PCT-US | 5480 |

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| EXAMINER | |
|---|---|
| HISSONG, BRUCE D | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1646 | |

| NOTIFICATION DATE | DELIVERY MODE |
|---|---|
| 07/14/2011 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

info@lmiplaw.com

| **Advisory Action Before the Filing of an Appeal Brief** | **Application No.** 10/590,421 | **Applicant(s)** FILPULA ET AL. |
|---|---|---|
| | **Examiner** Bruce D. Hissong, | **Art Unit** 1646 |

***--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --***

THE REPLY FILED 17 May 2011 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to or on the same day as filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires *6* months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☒ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☒ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☐ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: _____.
12. ☐ Note the attached Information *Disclosure Statement*(s). (PTO/SB/08) Paper No(s). _____
13. ☒ Other: See Continuation Sheet.

/Robert Landsman/
Primary Examiner, Art Unit 1647

Continuation of 13. Other: Claims 55, 57-58, 61-71, 80-86, 88-90, and 92-95 remain rejected under 35 USC 103 as being obvious in view of the combination of Drustrup (US 20030138403) and Durelli (The Lancet, 2002, Vol. 359, p. 1453-1460), as set forth on pages 2-5 of the office action mailed on 1/29/2011. In the response received on 5/17/2011, the Applicants have amended independent claim 55 to recite conjugation of IFN-b-1b to a polyalkylene oxide polymer having a molecule weight from about 30 kDa to about 40 kDa, and further amended the claim to require that the claimed conjugate retain at least about 20% of the antiviral activity relative to native IFN-b-1b, using the EMC/Vero or EMC/A549 antiviral assays. The Applicants first assert that the in the previous office action, the Examiner cites Durelli to argue that IFN-b-1b would have been known to be more potent/effective than IFN-b-1a for treatment of multiple sclerosis. The Applicants argue that in view of the dosing disparity (weekly vs daily for IFN-b-1a and -1b, respectively), it would be impossible to draw conclusions as to the relative potency of the two IFN analogs, and furthermore, a skilled artisan seeking a longer-acting conjugate would have looked to IFN-b-1a rather than IFN-b-1b. Additionally, the Applicants argue that the claims as amended require a specific level of retained antiviral activity, which is not taught or suggested by Durelli. The Applicants further argue that a person of oridnary skill in the art would have known of the teachings of Pepinsky and Runkell, and would have not expected that the less potent IFN-b-1b would have provided good kinetics and retention of potency relative to IFN-b-1b because Pepinsky showed that higher molecular weight conjugates had compromised bioactivity. Therefore, due to the different dosing schedules of Durelli and the fact that Durelli, as a source of the relative advantages of IFN-b-1a and IFN-b-1b, is silent as to the benefits of polyalkylene oxide polymer conjugation as it relates to retained antiviral activity, a person of oridnary skill in the art would not have sufficient motivation to conjugate PEG to IFN-b-1b as currently claimed. Finally, the Applicants argue that the specification provides test data that shows advantages and disadvantages of various composition parameters. Specifically, the Applicants argue that the specification shows that the claimed pH range resulted in no aggregation of PEG-IFN-b-1b, in contrast to higher pH values, and that the cited art would not have taught or suggested maing the compositions of the instant invention given these unexpected results and the unpredictability of the art of compositions and protein formulations.

These arguments have been fully considered and are not perusaive. Regarding Applicants arguments that the Examiner cited Durelli to illustrate that IFN-b-1b would have been known to be more potent/effective than IFN-b-1a, it is noted that Durelli was merely cited to show that IFN-b-1b was effective for treating multiple sclerosis, providing a person of oridnary skill in the art with the knowledge that IFN-b-1b is a potentially useful therapeutic protein. With regards to Applicants arguments that a person of ordinary skill in the art would look to IFN-b-1a rather than IFN-b-1b, it is noted that Durelli shows that both IFNs are useful for treating multiple sclerosis. Furthermore, Drustrup suggests that conjugation to a polyalkylene oxide polymer such as PEG would improve the pharmacological properties of IFN-b-1b because PEG conjugation is known to prolong serum half life. Thus, taken together, Drustrup and Durelli would show a skilled artisan that IFN-b-1b, although not as potent as IFN-b-1a, is effective for treating multiple sclerosis, and conjugation to PEG can improve its effectiveness. It is also noted that the claims do not require any level of IFN-b-1b potency/activity relative to IFN-b-1a. Furthermore, Drustrup teaches conjugates having a pH range which overlaps with the claimed pH range, and thus a skilled arisan would expect results such as those presented in the specification because these pH ranges are taught as preferred ranges. Finally, it is noted that the combination of Drustrup and Durelli provide a person of oridnary skill in the art with the knowledge of (a) an IFN-b-1b polypeptide that can be used to treate multiple sclerosis, and (b) a method of PEG conjugation which is commensurate with the instantly claimed method with regards to reagents and method steps, wherein such conjugation would improve the pharmacological properties of the resulting conjugate. It is also noted that because Drustrup teaches a method of PEG conjugation which is commensurate with the instant method, it would be expected that conjugating IFN-b-1b with Drustrup's method would inhernetly produce an IFN-b-1b conjugate which retains at least 20% of antiviral activity relative to native IFN-b-1b.